International Alliance for Biological Standardization

2nd IABS Workshop on Real World Evidence: Alternative Approaches to Phase 3 Clinical Trials for Vaccine Efficacy and Licensure: the role of Real World Evidence

December 10-11, 2025
Montreal, Canada

Title Evidence on vaccine benefit from Human Infection Models: insights and considerations

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Although the primary evidence for efficacy for full regulatory approval of the overwhelming majority of vaccines has been traditional large-scale Phase 3 field trials, **controlled human infection** is a feasible technique to help rule out or support likelihood of novel vaccine benefit. Human Infection models can be broadly classified into ***disease*** models, in which experimentally-inoculated participants experience disease symptoms as well as infection, and ***colonisation*** models in which participants become infected without the infection causing, or being permitted to cause, disease. For vaccine evaluation, the technique is particularly useful when natural disease is so sporadic as to render RCTs of vaccine efficacy unfeasible. A good example of this is the licensure of *Vaxchora* oral cholera vaccine in June 2016, using evidence of protection in a disease model of diarrhoea caused by an oral challenge with *Vibrio cholerae* in a relatively small cohort, together with extensive safety testing in larger groups of unchallenged volunteers. Human Infection Models are also useful to identify correlates of protection which can subsequently be used to measure efficacy in large scale population based studies. Controlled human infection models have assessed the role of multiple cell types (B cells, CD8+ T, T_{regs}, MAIT, Monocytes and DC) during *Salmonella Typhi* infection, showing that baseline antigen-specific responses can correlate with clinical outcomes. Using the same model, the Typbar-TCV typhoid conjugate vaccine was pre-qualified by the WHO in 2017 after a Phase 2b human challenge study demonstrated protection against a composite of fever and bacteraemia in healthy adult volunteers. Disease models have been extensively used commercially to down-select multiple vaccine candidates – good examples being malaria and influenza. More controversial is the use of colonization models to study diseases in which colonization of a mucosal site is a prerequisite to disease, eg nasopharyngeal colonization by *Streptococcus pneumoniae* or *Bordetella pertussis*, with the notion being that vaccines that inhibit colonization will reduce transmission (and thereby enhance herd immunity) as well as disease. A human controlled infection study showed that a glycoconjugate pneumococcal vaccine protected against pneumococcal colonization and reduced bacterial density. The pneumococcal model is currently being used to investigate pneumococcal vaccine in an African population in Africa- a site of high rates of disease incidence. My group has developed a *B.pertussis* human challenge model which has identified potential correlates of protection against infection and also been used to demonstrate that a live attenuated nasal vaccine can protect against *Bordetella* respiratory tract infection.

The **strength** of human controlled infection studies is that they permit prospective evaluation of human responses to defined challenges together with full characterization of the host and pathogen. The **weaknesses** include consideration of small cohort sizes, wider applicability, use of defined pathogens (usually a single strain) that may not be representative of all natural challenges, and participants who may not reflect the natural target population in diverse localities. Finally, such studies can only be conducted at specialist sites by highly trained staff.